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(54) Title: LOW RESIDUAL SOLVENT MICROSPHERES AND MICROENCAPSULATION PROCESS

(57) Abstract

This invention is the process for the preparation of microcapsules with a reduced residual solvent level, having a core compound encapsulated by a polymer coating which comprises, dissolving the polymer in an organic solvent in which the core compound is not soluble; adding the core compound; adding a first non-solvent of the polymer and core material selected from synthetic oil or vegetable oil in a ratio of first non-solvent to organic solvent of from about 1.5:1 wt/ wt to about 2.5:1 wt/wt to form microcapsules; and adding a second non-solvent of the polymer. The invention is als directed to microcapsules comprising a core compound encapsulated by a polymer coating, with the microcapsule having a residual solvent content of less than one percent. The invention is particularly useful for encapsulating pharmaceutical materials in biodegradable polymers.

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LOW RESIDUAL SOLVENT MICROSPHERES AND MICROENCAPSULATION PROCESS

FIELD OF INVENTION

The present invention relates to a method of microencapsulating a core material to form a microsphere with reduced residual solvent and water content.

BACKGROUND OF THE INVENTION

Microencapsulation is the process of coating a core material with a thin layer of a separate, encapsulating material to form microcapsules. The microencapsulation process has many applications, particularly in the pharmaceutical industry. In a pharmaceutical application, drugs are coated to obtain controlled-release of the drug, to improve chemical stability, and to permit the mixing and storage of reactive or incompatible drugs.

One of the methods of microencapsulation is a phase separation technique. For water-soluble or miscible core material, the phase separation process generally involves the technique of dispersing the solid core material of the desired particle size or an aqueous solution or suspension in a polymeric coating material dissolved in an organic solvent. The polymeric material is then deposited on the core material by gradual

precipitation of the polymer. This is achieved by either the use of precipitants, by changes in temperature, or by removal of the solvent by dilution or distillation. An example of this process is described in United States Patent No. 4,166,800 to Fong. In this patent, the polymer is precipitated by a phase separation agent, a non-solvent for the polymer.

U.S. Patent No. 4,518,547 to Cuff et al., describes a process for the microencapsulation of a hydrophilic core material by interfacial polycondensation. The process comprises dissolving the core material in a hydrophilic solvent, water, preferably together with an inert carrier material and adding a water immiscible organic solvent to form droplets containing the core material. Two complementary polycondensation monomer reactants are then added either sequentially or simultaneously which causes interfacial polymerization of a membrane encapsulating the core material.

U.S. Patent No. 4,384,975 to Fong describes an oil-in-water emulsion process for producing microspheres. This process comprises dissolving a polymer in a volatile, water-immiscible organic solvent in which the core material is not soluble; adding the core material; mixing the organic dispersion with an aqueous solution containing a carboxylic acid salt as the emulsifier to form a stable oil-in-water emulsion; and removing the organic solvent by evaporation to form the microcapsules.

U.S. Patent No. 4,389,330 to Tice et al., describes a process for preparing microcapsules containing a water insoluble core material. In this process, a polymer is dissolved in an organic solvent. The core material is dispersed or dissolved in the polymer-organic solvent.

This loaded mixture is then dispersed in a continuous-phase processing medium to form the microcapsules. The medium can be water or a non-aqueous media such as xylene or toluene or oils. The solvent is removed in a two-step removal process.

European Patent Application No. 81/305426.9 describes a microencapsulation process of water soluble polypeptides. In this procedure, a polymer, the wall-forming material, is dissolved in an organic solvent, methylene chloride. The core material is then added to the polymer-solvent solution. A non-solvent such as an oil compound which is soluble in the organic solvent, but is a non-solvent for the polymer is then added. In Example I, the ratio of non-solvent to organic solvent is about 1:3. The microcapsules that are formed are then quenched by mixing them with heptane.

With conventional phase separation encapsulation techniques, especially when used to microencapsulate a pharmaceutical water-soluble drug, there is a high solvent residue. A need, therefore, has continued to exist for a technique of preparing microcapsules and microspheres of high quality, with reduced residual solvent. Further, with microcapsules and microspheres encapsulated with biodegradable polymers, it is desirable to avoid water in the finished product in order to enhance product stability. Water present in the biodegradable polymers will typically cause the polymers to hydrolize; for example, the mechanism of biodegradation in polymers such as polylactides is by hydrolysis of ester linkages.

SUMMARY OF THE INVENTION

This invention comprises a process for microencapsulating a core material such that the resulting microcapsule has reduced residual solvent and reduced water content. In one embodiment of this invention, the microsphere has reduced residual solvent with no residual water present. The process of this invention involves the steps of:

(a) dissolving a polymeric coating material in an organic solvent in which the core material is not soluble;

(b) adding a core material;

(c) adding a first non-solvent of the polymer selected from synthetic oil or vegetable oil compounds in a ratio of first non-solvent to the organic solvent of from about 1:5 wt/wt to about 3:1 wt/wt to form embryonic microcapsules; and

(d) adding a second non-solvent of the polymer to harden the embryonic microspheres and to extract the first non-solvent from the microspheres.

The invention also comprises microspheres comprising a core material encapsulated by a polymer coating, the microspheres having a residual solvent content of about one percent.

The inventors have discovered that the use of synthetic oils or vegetable oil compounds as the first non-solvent in combination with the high ratio of the first non-solvent to the organic solvent for the polymeric coating material reduces the residual solvent in the final microsphere product. By use of this

invention it is possible to reduce the level of residual solvent in the microspheres.

In one embodiment of this invention, when solid particles to be encapsulated are used, the final microspheres will have a reduced residual solvent with no residual water content. Thus, the invention also comprises microspheres comprising a core material encapsulated by a polymer coating, the microspheres having a reduced residual solvent content of about one percent and with no residual water present.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The process of this invention is based on a phase separation technique to microencapsulate a core material. The general process of this invention involves the following steps:

(a) dissolving a polymeric coating material in an organic solvent;

(b) adding the core material as solid particles to form a suspension or as an aqueous solution to form a water-in-oil emulsion;

(c) adding a first non-solvent of the polymer, either synthetic oils or vegetable oils, in a ratio of first non-solvent to organic solvent of from about 1:5 wt/wt to about 3:1 wt/wt, to cause the polymer to precipitate onto the solid particles or around the water droplets to form embryonic microcapsules; and

(d) quenching with a second non-solvent of the polymer, to harden the microcapsules.

After the quenching step, the microsphere product is collected and dried under a vacuum to reduce the level of organic solvent in the final microsphere

product. By the process of this invention, a final microsphere product is produced that has a residual solvent level of less than one percent. By residual solvent is meant the level of residual second non-solvent that remains in the final microsphere product. There will also be a remaining amount of organic solvent that remains in the final microcapsule product, typically methylene chloride. The methylene chloride level is vacuum extractable to 0.1 % or less. As used herein, the ratios are based on a weight/weight ratio.

In the preferred embodiment of this invention, the general process of the invention involves the following steps:

(a) dissolving a polymeric coating material in an organic solvent;

(b) adding the core material as solid particles to form a suspension;

(c) adding a first non-solvent of the polymer, either synthetic oils or vegetable oils, in a ratio of first non-solvent to organic solvent of from about 1:5 wt/wt to about 3:1 wt/wt, to cause the polymer to precipitate onto the solid particles or around the water droplets to form embryonic microcapsules; and

(d) quenching with a second non-solvent of the polymer, to harden the microcapsules.

After the quenching step, the microsphere product is collected and dried under a vacuum to reduce the level of organic solvent in the final microsphere product. By the process of this invention wherein the core material is added as solid particles, a final microsphere product is produced that has a residual solvent level of less than one percent and a reduced water content.

The core material that may be used in this invention can include any material that is not soluble or miscible with the polymeric coating material or the organic solvent for the polymer or the first or second non-solvent for the polymer.

The polymeric coating material that may be used in this invention may be either natural or synthetic polymers, or combinations thereof. The polymers may include cellulosic polymers, polyvinyl acetate, polyvinyl alcohol, polyvinyl chloride, natural and synthetic rubbers, polyacrylates, polyorthoesters, and the like.

Specific examples include polystyrene, ethylcellulose, cellulose acetate, hydroxy propylmethyl cellulose, cellulose acetate, dibutylaminohydroxypropyl ether, polyvinyl butyral, polyvinyl formal, poly(meth)acrylic acid ester, polyvinylacetal-diethylamino acetate, 2-methyl-5-vinyl pyridine, methacrylate-methacrylic acid copolymer, polycarbonate, polyesters, polypropylene, vinylchloride-vinylacetate copolymer, polysaccharides, and glycerol distearate.

Suitable polymers for use with a pharmaceutical core material include biodegradable polymers such as polyanhydrides and aliphatic polyesters including polylactide, polylactide-co-glycolide polyglycolide, polycaprolactone, polylactide-co-caprolactone, polyhydroxybutyride, polyanhydride, polydioxanone, and copolymers thereof such as poly(lactide-co-glycolide) copolymer and polylactide homopolymer.

The organic solvent that may be used according to this invention to dissolve the polymeric coating material must be a material which will dissolve the polymeric coating material and which will not dissolve the core material to be encapsulated. If the core

material is a pharmac utical compound, then the rganic solvent must also be chemically inert with respect to any pharmaceutical compounds to be encapsulated.

The organic solvent can be selected from a variety of common organic solvents including halogenated aliphatic hydrocarbons, typically the C_1 to C_4 halogenated alkanes, such as, for example, chloroform, methylene chloride, ethylene dichloride, ethylene chloride, ethyl acetate, methylchloroform and the like; aromatic hydrocarbon compounds, halogenated aromatic hydrocarbon compounds; cyclic ethers such as tetrahydrofuran and the like.

The first non-solvent for the polymer according to this invention may be selected from synthetic oils or vegetable oil compounds. Synthetic oils may include silicone oil, mineral oil, and petroleum oils. Vegetable oils may include sesame oil, peanut oil, soybean oil, corn oil, cotton seed oil, coconut oil, linseed oil, and other related oils. By non-solvent is meant a solvent that is miscible with the organic solvent but is not a solvent for the polymeric coating or core material. The inventors have discovered that the amount and type of the first non-solvent for the polymer controls the level of residual solvent (second non-solvent) in the final microsphere product. According to this invention, the ratio of first non-solvent to organic solvent is from about 1:5 to about 3:1. Further, in one embodiment of this invention, by employing solid drug particles rather than aqueous solutions or suspensions of drug, no residual water is present in the final product.

The polymeric coating material is dissolved in the selected organic solvent prior to adding the core

material. The amount of polymeric coating material dissolved in the solvent is typically from about 5 to 50 percent.

The core material is then added to the polymer-solvent solution, preferably, as solid particles to form a suspension or as an aqueous solution to form a water-in-oil emulsion. The amount of core material added to the polymer-solvent solution is not critical, although the ratio of core material to polymer is important insofar as that at too high an amount of core material to polymer, microspheres will not form. Typically, the upper limit of the ratio of core material to polymer may be about 80 parts by weight core material to about 20 parts by weight polymer. There is no lower limit to the ratio at which the core material can be combined with the polymeric coating material, except that at very low loadings of core material in the microcapsules, the microcapsules would not be practically useful.

Typically in the process of this invention, core material is added to the polymer-solvent solution such that the core material comprises about 5 to 50 weight percent.

The first non-solvent, synthetic oil or vegetable oil, in an amount of the ratio of about 1:5 to about 3:0, first non-solvent to organic solvent, is then added slowly to the mixture of polymeric solvent solution with the added core material. The first non-solvent causes the polymeric material to precipitate out of the organic solvent onto the core material, thereby encapsulating the core material. The first non-solvent is added under carefully controlled conditions of temperature, rate, and stir speed. For example, temperature conditions may range from -20 degrees C to +30 degrees C; rate 5

g/minutes per g f batch; stir speed from 400 to 2500 rpm.

Following the isolation of the microspheres, the microspheres are treated in a quenching step to harden them. In this step, the microspheres are quenched with a second non-solvent. This second non-solvent hardens the microspheres and extracts the solvent from the microspheres and yet does not dissolve the microspheres (wall material or core material).

The amount of second non-solvent added in this quenching step is typically from about 0.25 l/g of batch to about 1 l/g of batch. Suitable second non-solvents include heptane and aliphatic hydrocarbons such as hexanes.

After the solvent has been removed from the microspheres, the microspheres are isolated, such as by filtration or sieving, and are dried by exposure to air or by other conventional drying techniques, such as vacuum drying, drying over a dessicant, or the like. Preferably, the microspheres are dried under a vacuum at room temperature to further reduce the level of organic solvent in the final microsphere product.

As has been found from experimentation, in conventional phase-separation techniques, 5 to 10% residual solvent (heptane) is usually present in the finished product. By the process according to this invention, the residual solvent content is about one percent.

Thus, by the process of this invention a final microsphere product is produced that contains about one percent residual solvent. In the preferred embodiment, the final microsphere product contains about one percent residual solvent with no residual water present. The microsphere product of the present invention is usually

made up of particles of a spherical shape although sometimes the microspheres may be irregularly shaped. The microspheres can vary in size, ranging from submicron to millimeter diameters. Preferably, submicron to 250 um diameters are desirable for pharmaceutical formulations allowing administration of the microspheres with a standard syringe and needle. The microspheres find utility in a wide variety of applications depending upon the encapsulated core compound. Advantageously, the microsphere product, according to this invention, is an encapsulated pharmaceutical compound which can be administered to both humans and animals.

The core material that may be used in the process of this invention may include agricultural agents, such as insecticides, fungicides, herbicides, rodenticides, pesticides, fertilizers, and viruses for crop protection and the like; cosmetic agents, such as deodorants, fragrances, and the like; food additives such as flavors; and pharmaceutical agents.

Pharmaceutical compounds are the preferred core materials of the process according to this invention. These compounds may also include the non-toxic pharmaceutically acceptable acid addition salts, such as hydrochloride, sulfate, phosphate, succinate, benzoate, acetate, pamoate, fumerate, mesylate, and the like. Among the pharmaceutical drugs which may be utilized are the following: contraceptive agents including estrogens such as diethyl stilbestrol, 17-beta-estradiol, estrone, ethinyl estradiol, mestranol, and the like; progestins such as norethindrone, norgestryl, ethynodiol diacetate, lynestrenol, medroxyprogesterone acetate, dimethisterone, megestrol acetate, chlormadinone acetate, norgestimate, norethisterone, ethisterone, melengestrol,

norethynodrel and the like; and spermicidal compounds such as nonylphenoxypolyoxyethylene glycol, benzethonium chloride, chlorindanol and the like. Other biologically active agents which can be incorporated in the present microcapsules include gastrointestinal therapeutic agents such as aluminum hydroxide, calcium carbonate, magnesium carbonate, sodium carbonate and the like; non-steroidal antifertility agents; parasympathomimetic agents; psychotherapeutic agents; major tranquilizers such as chloropromazine HCl, clozapine, mesoridazine, metiapine, reserpine, thioridazine and the like; micro tranquilizers such as chlordiazepoxide, diazepam, meprobamate, temezepam and the like; rhinological decongestants, sedative-hypnotics such as codeine, phenobarbital, sodium pentobarbital, sodium secobarbital and the like; other steroids such as testosterone and testosterone propionate; sulfonamides; sympathomimetic agents; vaccines; vitamins and nutrients such as the essential amino acids, essential fats and the like; antimalarials such as 4-aminoquinolines, 8-amino-quinolines, pyrimethamine and the like; anti-migraine agents such as mazindol, phentermine and the like; anti-Parkinson agents such as L-dopa; anti-spasmodics such as atropine, methscopolamine bromide and the like; anti-spasmodics and anticholinergic agents such as bile therapy, digestants, enzymes and the like; anti-tussives such as dextromethorphan, noscapine and the like; bronchodilators, cardiovascular agents such as anti-hypertensive compounds, Rauwolfia alkaloids, coronary vasodilators, nitroglycerin, organic nitrates, penta-erythritotetranitrate and the like; electrolyte replace-ments such as potassium chloride, ergotalkaloids such as ergotamine with and without caffeine, hydrogenated ergot

alkaloids, dihydroergocristine methanesulfate, dihydroergocornine methanesulfonate, dihydroergokroyptine methanesulfate and combinations thereof, alkaloids such as atropine sulfate, Belladonna, hyoscine hydrobromide and the like; analgetics; narcotics such as codeine, dihydrocodienone, meperidine, morphine and the like; non-narcotics such as salicylates, aspirin, acetaminophen, d-propoxyphene and the like; antibiotics such as the cephalosporins, chloranphenical, gentamicin, Kanamycin A, Kanamycin B, the penicillins, ampicillin, streptomycin A, antimycin A, chloropamtheniol, metromidazole, oxytetracycline penicillin G, the tetracyclines, and the like; anti-cancer agent; anti-convulsants such as mephenytoin, phenobarbital, trimethadione; antiemetics such as thietylperazine; antihistamines such as chlorophinazine, dimenhydrinate, diphenhydramine, perphenazine, tripelennamine and the like; anti-inflammatory agents such as hormonal agents, hydrocortisone, prednisolone, prednisone, non-hormonal agents, allopurinol, aspirin, indomethacin, phenylbutazone and the like; prostaglandins; cytotoxic drugs such as thiotepa, chlorambucil, cyclophosphamide, melphalan, nitrogen mustard, methotrexate and the like; antigens of such microorganisms as Neisseria gonorrhea, Mycobacterium tuberculosis, Herpes virus (humonis, types 1 and 2), Candida albicans, Candida tropicalis, Trichomonas vaginalis, Haemophilus vaginalis, Group B streptococcus E. coli, Strep. mutans, Microplasma hominis, Hemophilus ducreyi, Granuloma inguinale, Lymphopathia venereum, Treponema pallidum, Brucella abortus, Brucella melitensis, Brucella suis, Brucella canis, Campylobacter fetus, Campylobacter fetus intestinalis, Leptospira pomona, Listeria moncytogenes, Brucella ovis, Equine herpes

virus 1, Equine arteritis virus, IBR-IBP virus, BVD-MB virus, Chlamydia psittaci, Trichomonas foetus, Toxoplasma gondii, Escherichia coli, Actinobaccillus equuli, Salmonella abortus ovis, Salmonella abortus equi, Pseudomonas aeruginosa, Corynebacterium equi, Corynebacterium pyogenes, Actinobaccilus seminis, Mycoplasma bovigenitalium, Aspergillus fumigatus, Absidia ramosa, Trypanosoma equiperdum, Babesia caballi, Clostridium tetani, and the like; antibodies which counteract the above microorganisms; and enzymes such as ribonuclease, neuramidinase, trypsin, glycogen phosphorylase, sperm lactic dehydrogenase, sperm hyaluronidase, adenossine-triphosphatase, alkaline phosphatase, alkaline phosphatase esterase, amino peptidase, trypsin chymotrypsin, amylase, muramidase, acrosomal proteinase, diesterase, glutamic acid dehydrogenase, succinic acid dehydrogenase, betaglycophosphatase, lipase, ATP-ase alpha-peptate gama-glutamylotranspeptidase, sterol-3-beta-ol-dehydrogenase, DPN-di-aprorase.

Other compounds of particular interest are hormonally active polypeptides, especially luteininzing hormone-releasing hormone (LR-RH) polypeptides, analogues, and antagonists thereof; mammalian growth hormones, including human, bovine, equine, and sheep growth hormones; alpha, beta, gamma, and omega interferon; interleukin I and interleukin II; and erythropoietin.

Having generally described the invention, further understanding can be obtained by reference to certain specific examples which are provided herein for purpose of illustration only and are not intended to be limiting unless otherwise specified.

EXAMPLE I

This example describes the procedure for preparing microspheres, varying the ratio of the first non-solvent, silicone oil, to the organic solvent, methylene chloride.

The polymeric coating material, a copolymer with a 50:50 molar ratio of lactide:glycolide units with inherent viscosity of 0.69 dl/g, was weighed and dissolved in methylene chloride (CH_2Cl_2). The encapsulate, histrelin, was dispersed in the solvent/polymer mixture using a stirrer. With continued stirring, silicone oil was added to the mixture. The ratio of the silicone oil to the methylene chloride solvent was varied in these experiments and the results are shown in the following Table 1. The silicone oil caused the polymer to phase separate, and deposit as droplets of solvent-fluid polymer onto the surface of the water-soluble microdroplets. These solvent-fluid polymer droplets then coalesced to form a continuous film around the water-soluble microdroplets.

The microspheres were then hardened by quenching by pouring the contents of this first mixture into a beaker containing heptane. The heptane/methylene chloride/-silicone oil solution was removed by filtration. The microspheres were further washed with aliquots of heptane. The microspheres were dried at room temperature under vacuum. The microspheres obtained from this preparation were determined to have diameters ranging in size from 25 to 150 microns.

The following Table 1 gives the results of the testings to show the effect of the ratio of silicone oil to methylene chloride and the effect of the viscosity of

the silicon il. Th viscosity f the silicone oil was studied at 200cs, 350cs, and 500cs. In three of the tests, histrelin was used as the encapsulate; with the other tests a placebo was used.

TABLE 1

SiO_2 Oil : CH_2Cl_2 vs. % Residuals

Viscosity of SiO_2	Encapsulate	wt/wt Ratio of SiO_2 Oil: CH_2Cl_2	% Residual Heptane (C_7H^{16})	% Residual Methylene Chloride (CH_2Cl_2)*
350cs	loaded**	1:2.6	8.7	4.8
	loaded	1:1	3.3	5.0
	loaded	1.9:1	0.9	4.9
350cs	placebo	2:1	0.9	5.1
	placebo	2:1	1.1	3.9
200cs	placebo	2:1	0.8	4.4
500cs	placebo	1:1	3.1	4.3
	placebo	2:1	0.8	3.7

* Vacuum extractable to 0.8%
** Loaded encapsulate = histrelin

EXAMPLE II

Silicone Oil 1:2.6 Ratio (wt/wt) of First Non-Solvent to Solvent

A 50:50 lactide:glycolide copolymer, 1.80 g, was dissolved in 15.7 g of methylene chloride and charged to a 100 ml flask. Histrelin, 200.4 mg, was suspended in 12.2 g of methylene chloride and added with stirring to the polymer solution. An additional 6.0 g of methylene chloride was then added (total = 33.9 g). Silicone oil

(350 cs), 13.13 g was added over 8.5 minutes. Then, the contents of the reaction flask were transferred to 2800 ml of n-heptane with stirring at 21°C. Stirring was continued for 3 hours. The microspheres were collected on stainless-steel sieves and allowed to air dry. The residual heptane content was found to be 8.7% by weight. The histrelin content was 7.76% by weight.

EXAMPLE III

Silicone Oil 1.9:1 Ratio of First Non-Solvent to Solvent

1.8 g of a 50:50 lactide:glycolide copolymer was dissolved in 15.0 g of methylene chloride. Histrelin, 201.5 mg, was suspended in 15.0 g of methylene chloride and sonicated briefly to disperse the drug. The dispersion was then added with stirring to the polymer solution. An additional 12.67 g of methylene chloride was added to the reaction flask. Silicone oil (350 cs), 82.17 g, was added over 13 minutes. The contents of the reaction flask were transferred to 3250 ml of n-heptane with stirring at 18.2°C. Stirring was continued for 3 hours. The microcapsules were collected on stainless-steel sieves and allowed to air dry. Residual heptane was found to be 0.9% by weight. Histrelin content was 8.35% by weight.

The foregoing invention has been described in some detail by way of illustration and example for purposes of clarity and understanding. It will be obvious that certain changes and modifications may be practiced within the scope of the invention, as limited only by scope of the appended claims.

WHAT IS CLAIMED IS:

1. A process for the preparation of microspheres comprising a core material encapsulated by a polymer coating comprising:

(a) dissolving a polymer coating material in an organic solvent in which the core material is not soluble to form a polymer-organic solvent mixture;

(b) adding the core material to said mixture;

(c) adding a first non-solvent of the polymer selected from synthetic oil or vegetable oil in a ratio of first non-solvent to organic solvent of from about 1.5:1 wt/wt to about 3:1 wt/wt to the core material-containing mixture to form embryonic microspheres; and

(d) quenching said embryonic microspheres with a second non-solvent of the polymer to produce microspheres.

2. The process of claim 1 wherein said polymer coating material is selected from the group consisting of cellulosic polymers, polyvinyl acetate, polyvinyl alcohol, polyvinyl chloride, natural and synthetic rubbers, polyacrylates and polyorthoesters.

3. The process of claim 1 wherein said polymer coating material is selected from the group consisting of polystyrene, ethylcellulose, cellulose acetate, hydroxy propylmethyl cellulose, cellulose acetate, dibutylaminohydroxypropyl ether, polyvinyl butyral, polyvinyl formal, poly(meth)acrylic acid ester, polyvinylacetal-diethylamino acetate, 2-methyl-5-vinyl pyridine, methacrylate-methacrylic acid copolymer, polycarbonate, polyesters, polypropylene, vinylchloride-

vinylacetate copolymer, polysaccharides, and glycerol distearate.

4. The process of claim 1 wherein said polymer coating material is a biodegradable polymer selected from the group consisting of polylactide, polylactide-co-glycolide polyglycolide, polycaprolactone, polylactide-co-caprolactone, polyhydroxybutyride, polyanhydride, polydioxanone, and copolymers thereof.

5. The process of claim 1 wherein the polymer coating material is a selected from the group consisting of poly(lactide-co-glycolide) and polylactide.

6. The process of claim 1 wherein said organic solvent is selected from chloroform, methylene chloride, tetrahydrofuran, and ethyl acetate.

7. The process of claim 1 wherein said first non-solvent is selected from silicone oil, mineral oil, petroleum oil, sesame oil, peanut oil, soybean oil, corn oil, cotton seed oil, coconut oil, and linseed oil.

8. The process of claim 6 wherein said first non-solvent is sesame oil or silicone oil.

9. The process of claim 1 wherein said second non-solvent is selected from heptane, hexanes or pentane.

10. The process of claim 1 wherein said core material comprises solid particles and is added to said mixture in step (b) to form a suspension.

11. The process of claim 1 wherein said core material comprises an aqueous solution and is added to said mixture in step (b) to form a water-in-oil emulsion.

12. The process of claim 1 further comprising treating said microsphere product by drying said microsphere product under a vacuum.

13. A process for producing microspheres comprising a core material encapsulated by a polymer coating wherein said microspheres contain less than one percent residual solvent and with no residual water content, comprising:

(a) dissolving a polymer coating material in an organic solvent in which the core material is not soluble to form a polymer-organic solvent mixture;

(b) adding the core compound as solid particles to said mixture to form a suspension;

(c) adding a first non-solvent of the polymer selected from synthetic oil or vegetable oil in a ratio of first non-solvent to organic solvent of from about 1.5:1 wt/wt to about 3:1 wt/wt to the core material-containing mixture to form embryonic microcapsules; and

(d) quenching said embryonic microcapsules with a second non-solvent of the polymer to produce a final product containing about one percent residual solvent.

14. Microcapsules produced by the process of any of claims 1-13.

15. A microsphere comprising a core material encapsulated by a polymer coating, said microsphere having a residual solvent content of one percent or less.

16. The microsphere of claim 15 wherein said polymer is selected from the group consisting of cellulosic polymers, polyvinyl acetate, polyvinyl alcohol, polyvinyl chloride, natural and synthetic rubbers, polyacrylates and polyorthoesters.

17. The microsphere of claim 15 wherein said polymer is selected from the group consisting of polystyrene, ethylcellulose, cellulose acetate, hydroxy propylmethyl cellulose, cellulose acetate, dibutylamino-hydroxypropyl ether, polyvinyl butyral, polyvinyl formal, poly(meth)acrylic acid ester, polyvinylacetal-diethylamino acetate, 2-methyl-5-vinyl pyridine, methacrylate-methacrylic acid copolymer, polycarbonate, polyesters, polypropylene, vinylchloride-vinylacetate copolymer, polysaccharides, and glycerol distearate.

18. The microsphere of claim 15 wherein said polymer is a biodegradable polymer selected from the group consisting of polylactide, polylactide-co-glycolide polyglycolide, polycaprolactone, polylactide-co-caprolactone, polyhydroxybutyride, polyanhydride, polydioxanone, and copolymers thereof.

19. The microsphere of claim 15 wherein said core material is a luteinizing hormone-releasing hormone (LH-RH) peptide, analog, or antagonist.

20. The microsphere of claim 15 wherein said core material is growth hormone.

21. The microsphere of claim 15 wherein said core material is alpha, beta, gamma, or omega interferon.

22. The microsphere of claim 15 wherein said core material is erythropoietin.

23. The microsphere of claim 15 wherein said core material is interleukin I or interleukin II.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/03859

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61K 9/50, 9/52; B01J 13/02

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	264/4.3, 4.32; 427/213.31, 213.32

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

Messenger Text Search

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X Y	US, A, 4,673,595 (ORSOLINI) 16 June 1987, see column 2, lines 28 to 66, column 3, lines 18 to 67, and all of column 4.	15, 17 - 21 1 - 23
X Y	US, A, 4,675,189 (KENT) 23 June 1987, see the entire document.	1 1 - 21
Y P	US, A, 4,711,782 (OKADA) 8 December 1987, see column 1, lines 44 to 63, column 2, lines 49 to 66, column 4, lines 35 to 50, column 5, lines 6 to 27, and column 14, line 38 bridging column 15, line 15.	19-23
X P	US, A, 4,766,012 (VALENTI) 23 August 1988, see column 2, lines 39 and 40, column 3, lines 32 to 40, column 4, lines 6 to 28, column 5, lines 37 to 54, column 7, lines 43 to 57, and column 8, lines 23 to 39.	15-17
X	US, A, 4,389,331 (SAMEJIMA) 21 June 1983, see column 2, lines 5 to 22, and lines 36 to 68, column 5, lines 1 to 25, and column 6, lines 35 to 44.	15-17

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17 JANUARY 1989	08 MAR 1989
International Searching Authority	Signature of Authorized Officer
ISA/US	JOHN M. COVERT

Form PCT/ISA/210 (second sheet) (Rev.11-87)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	US, A, 4,389,330 (TICE) 21 June 1983, see the entire document.	1 - 14
Y P	US, A, 4,741,872 (DELUCA) 3 May 1988, see column 4, lines 46 to 64, column 6, line 64 bridging column 7, line 9, and column 8, lines 53 to 66.	14,15,19,20, 21,22,23
Y	US, A, 4,479,911 (FONG) 30 October 1984, see column 4, line 49 bridging column 5, line 7, and column 5, lines 25 to 58.	15 - 18
X Y	US, A, 4,244,836 (FRENSCH) 13 January 1981, see column 2, lines 55 to 65, column 5, line 26 bridging column 6, line 31.	15 16
A	US, A, 3,773,919 (BOSWELL) 20 November 1973, see column 10, lines 23 to 37.	
A	US, A, 3,971,852 (BRENNER) 27 July 1976, see column 12, lines 10 to 56, and column 13, lines 1 to 25.	
A P	US, A, 4,713,249 (SCHRODER) 15 December 1987, see column 2, lines 46 to 53, column 3, line 59 bridging column 4, line 20, and column 4, line 65 bridging column 5, line 27.	
A	US, A, 4,637,905 (GARDNER) 20 January 1987, see column 3, lines 43 to 48, and column 4, lines 1 to 56.	
Y	EP, A, 052,510 (SYNTEX) 28 May 1982, see the entire document.	1 - 14